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Award Number: DAMD17-98-1-8240

TITLE: Weight Gain in Breast Cancer Patients on Chemotherapy: Exploring Hormonal Body Composition and Behavioral Mechanisms

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REPORT DATE: September 1999

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	September 1999	Annual (1 Sep 98 - 31 Aug 99)

4. TITLE AND SUBTITLE
Weight Gain in Breast Cancer Patients on Chemotherapy: Exploring Hormonal Body Composition and Behavioral Mechanisms

5. FUNDING NUMBERS
DAMD17-98-1-8240

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT ***(Maximum 200 Words)*** **Purpose:** The purpose of this study is to prospectively and systematically observe the relative contribution of each viable mechanism such as nutritional intake, activity levels, body composition, hormonal function, thyroid function, coping mechanisms and fatigue scores during chemotherapy on weight gain in breast cancer patients. If changes in the above factors contribute to weight gain and thus alter prognosis, manipulation of these variables by timely intervention may improve prognosis and facilitate recovery from breast cancer.

Progress: As planned and described in the Statement of Work, Task 1 of recruitment and data collection and Task 2 - abstraction of Medical record data during months 1-30, of which moths 0-12 is currently reported, has been successful, thus far. Currently 63 subjects have been recruited, 30 completed, 26 active, 7 dropouts, five (5) of who did not wish to participate and 2 were eliminated, as the final treatment plan did not include adjuvant chemotherapy. All data were collected from the current sample, including blood sample for hormonal assays. In addition to the proposed study, a structured "Moffitt Weight Management Program", has been established for this group, post-treatment Data entry and analysis of preliminary data will be initiated in November 1999, and outcomes will be reported at that time.

14. SUBJECT TERMS
Breast Cancer, Chemotherapy, weight gain, hormones, treatment effects

15. NUMBER OF PAGES
10

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

FOREWORD

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N/A In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

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Dagi B. Dhuwar 10/6/99

PI - Signature Date

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Introduction:

Weight Gain in Breast Cancer Patients on Chemotherapy

It is estimated that over 181,600 new cases of female breast cancer will be diagnosed in the United States in 1997 and 44,190 will die of this disease.[1] Most of these patients will be diagnosed with stage I or II disease, and a significant proportion of these women will be treated with chemotherapy in addition to surgery and/or radiation therapy. Although the benefits of adjuvant chemotherapy and radiation therapy are well established, and although several side effects such as cancer cachexia challenge the health professionals, one of the most distressing side effect as reported by patients is weight gain.[2-8] Weight gain in this population may prove to be a more serious side effect than others, since it can not only decrease quality of life but may potentially increase rate of recurrence and threaten long-term survival.[7, 9-11] The impact of weight gain may be even more profound, because it may predispose women to heart disease, diabetes, gall bladder disease, endometrial cancer and orthopedic disturbances. These chronic illnesses may pose a greater concern, since women with early stage breast cancer will be cured of the disease but may suffer long term negative consequences as a result of treatment.

Prevalence and Magnitude of Weight Gain in Breast Cancer Patients During Chemotherapy: Weight gain, anywhere from 5-50lbs in breast cancer patients receiving adjuvant therapy has now been documented consistently for the past two decades.[12-13] Significant weight gain occurred in 50-96% of all breast cancer patients receiving adjuvant chemotherapy[3] irrespective of stage of disease, more so among premenopausal women compared to post menopausal women.[9] In addition, significant gain in weight has been observed in patients receiving prednisone as a chemotherapeutic regimen[14-15] or when multiple agents are used[10, 12] compared to single agent therapies. Bonadonna et al found that longer duration of chemotherapy increased the total amount of weight gained[16] and oral agents produce greater weight gains than infusion-based therapies.[17]

Consequences of Weight Gain: More recent findings suggest that obesity at time of diagnosis is an adverse prognostic indicator even after the administration of chemotherapy.[18] We and other have observed that obesity in postmenopausal node positive patients was a negative prognostic indicator[15, 19] and the risk for disease recurrence among obese patients was 1.33-1.5 times that of the non-obese population.[9, 18] Camoriano, in addition reported 1.6 times greater risk of death in premenopausal women who gained weight.[9]

Possible Mechanisms: While the cause of weight gain in breast cancer patients remains unknown it, is most likely a result of several contributing factors. Some proposed explanations include psychological factors such as change in coping mechanisms leading to a change in eating behavior, change in activity level due to fatigue or disruption of normal lifestyle, hormonal changes, and the metabolic effects of chemotherapy or radiotherapy.

Purpose:

The purpose of this study is to prospectively and systematically observe the relative contribution of each viable mechanism such as nutritional intake, activity levels, body composition, hormonal function, thyroid function, coping mechanisms and fatigue scores on weight gain in breast cancer patients on chemotherapy.

Objectives

Specific Aim 1: To characterize the severity and course of weight gain among women undergoing adjuvant chemotherapy.
Specific Aim 2: To examine the impact of chemotherapy-induced change in activity levels on weight gain among women undergoing adjuvant chemotherapy.
Specific Aim 3: To examine the effect of chemotherapy-induced hyperphagia on weight gain among women undergoing adjuvant chemotherapy.
Specific Aim 4: To examine the effect of chemotherapy-induced sex-hormone level changes on weight gain among women undergoing adjuvant chemotherapy.
Specific Aim 5: To examine the effect of chemotherapy-induced change in thyroid function on weight gain among women undergoing adjuvant chemotherapy.
Specific Aim 6: To systematically investigate the relative contribution of thyroid function, sex-hormonal levels, physical activity, body composition, psychological state and nutritional intake on changes in body weight in a group of pre-menopausal and post-menopausal stage I-III breast cancer patients, receiving adjuvant chemotherapy.

Key Research Accomplishments:

As planned and described in the Statement of Work, Task 1 of recruitment and data collection and Task 2 - abstraction of Medical record data during months 1-30, of which moths 0-12 is currently reported, has been successful, thus far.. The first two months of the study was spent organizing (a) Instruments and procedures to be used in the study, (b) Consent form and procedures, (c) establishing procedures for recruitment from various medical oncology clinics at the cancer Center, (d) timely, safe blood draws thus preventing duplication of draws, (d) preventing any additional patient visit to the center, (e) collaboration with lab to plan for safe, accurate and timely handling of blood and transport.

Task 1: Subject Recruitment: The patient sample selected for the study is to include a total of 200 consecutive pre-menopausal and post-menopausal patients recruited over a 27 month period, with primary, operable, Stage I to IIIB, axillary lymph node positive and negative breast cancer patients who have consented to be treated using one of two adjuvant or systemic chemotherapy protocols at the H. Lee Moffitt Cancer Center & Research Institute during the study period. Women, of all races and ethnicity, between ages 25 and 75, and breast cancer patients who will receive at least 75% Cytoxan, Methotextrate, 5FU (CMF), Cytoxan, Cytoxan, Adriamycin and 5FU(CAF) or Cytoxan and Adriamycin (CA) chemotherapy regimens with or without radiation therapy at first screening contact will be admitted to the study. Currently 63 subjects have been recruited, of whom 30 have completed the 6 month treatment/observation phase of the study, and an additional 26 subjects are currently active in this protocol. As predicted we had seven(7) dropouts in the study, five(5) of whom did not wish to participate and 2 were eliminated from the study as the final treatment plan did not include adjuvant chemotherapy. We have thus successfully recruited 32% of the sample planned for the study, in a period of 10 months.
Data Collection: Upon recruitment, and upon receiving consent from subjects, the following data were collected, as planned:
1.Confirmation of the accuracy of eligibility information, including the using an initial screening form.

2.Demographic information, personal and medical history, hormonal and reproductive history, exercise, smoking and alcohol use history will be obtained by an RD using the Epidemiological Questionnaire.
3.Anthropometric measurements such as subject's height, weight, skinfolds and circumference measurements.
4.Twenty (20) ml of blood will be drawn into heparinized tubes in a non-fasting state at the same time of day, between 7:00 AM and 12:00 noon, for each individual to obtain 10 ml of serum for analysis of total and free estradiol, sex-hormone binding globulin, T4 and thyroid binding globulin assessment for T3 uptake.
5.Subjects will be asked to complete a self-administered version of the Stanford-five city Project Questionnaire to monitor Activity Levels.
6. Standard 4-day diet record(FDFR).
7. Menstrual histories will be obtained from all peri- and pre-menopausal subjects. This information will be recorded on the FDFR.
8.The Profile of Mood States Fatigue Subscale (POMS-F), a scale to measure fatigue (Appendix 6) will be used to quantify fatigue in these subjects.[37]
9.The Ways of Coping Checklist (WOCC) consists of 66 items that describe a broad range of cognitive and behavioral strategies people use to manage internal and/or external demands in specific stressful encounters defined here as breast cancer treatment, will be used.[38]

We have observed that several patients have had difficulty completing the 4-day food records during the 3 to 4 chemotherapy treatments. During those situations, the research team has been able to obtain a 24-hour recall or a 2-day record of intake from the patient or a family member. Apart from this instrument, we have had excellent compliance to completion of serial information from our breast cancer patients.

Task 2: Abstraction of Medical Record Data:
Upon completion of the study, data regarding patient's disease related prognostic indicators is currently being extracted from their medical chart. Quality control procedures for data collection and abstraction have been ongoing. We are currently continuing to obtain information on tumor size, ER/PR positivity, DNA ploidy status and proliferative indices such as Ki-67, which are routinely available for this population.

Nutritional Intervention in Patients post completion of the study period:
Upon completion of the study, we have felt the need for and have had several requests from medical oncologists and patients for continued follow-up of patients who have gained weight during chemotherapy. We have established a structured "Moffitt Weight Management Program", which is currently offered as a pilot program, specifically for this post-treatment Breast Cancer Patient group to enable them to successfully manage weight, post-treatment. The program includes 8-1 hour sessions and incorporates body composition and nutritional analysis, Behavior Management, Assessing fitness and incorporating physical activity and improving food choices towards long-term weight management.

Data Entry & Analysis:

We plan to initiate data entry within the month of November 1999. Quality control procedures for data entry will be applied., as planned.

Reportable Outcomes:
As data entry nor analysis has not been initiated, there is no reportable outcomes at this time.

Conclusions:
Definitive prospective studies that systematically observes the relative contribution of each viable mechanism such as nutritional intake, activity levels, body composition, hormonal function, thyroid function, coping mechanisms and fatigue scores during chemotherapy on weight gain are needed. While it is important to initiate action to prevent the problem of weight gain in breast cancer patients, an essential first step to intervention or rehabilitation is to identify the mechanisms by which weight gain occurs which may hasten the development of effective intervention strategies for weight management for specific regimens. In our current longitudinal research study, we are exploring the impact of adjuvant chemotherapy for breast cancer treatment on these clinical and psychological outcomes and identify systematically the mechanisms and offer opportunities for delivering effective care to prevent and facilitate recovery from breast cancer. If changes in body weight, body composition, hormonal levels, psychological health, dietary and other lifestyle factors alter prognosis, manipulation of these variables by intervention and counseling may improve prognosis, facilitate recovery from breast cancer and the credibility of such interventions will be enhanced.

Based on the relevant literature and the results of our pilot study, we hypothesize that weight gain will occur in a significant number of breast cancer patients on adjuvant chemotherapy and in addition that this weight gain will be a result of hyperphagia, significant lowering of activity level, decrease in free and total estradiol levels, similar to the hormonal milieu of menopause which is known to alter body composition and appetite and lowering of thyroid function resulting in decreased activity levels, all contributing to weight gain in this population. The purpose of the current study is to explore the impact of adjuvant chemotherapy for breast cancer treatment on these clinical and psychological outcomes and identify systematically the mechanisms and offer opportunities for delivering effective care to prevent and facilitate recovery from breast cancer, which will further the programmatic goals of the BCRP of the Department of Defense. Our research may in addition lead to the elucidation of hormonal markers that predict the probability of disease recurrence. This may also establish the mechanisms by which weight gain has an impact on the neoplastic process. If changes in body weight, body composition, hormonal levels, psychological health, dietary and other lifestyle factors alter prognosis, manipulation of these variables by intervention and counseling may improve prognosis, facilitate recovery from breast cancer and the credibility of such interventions will be enhanced.

Bibliography

1. American Cancer Society,Inc. (1997). Cancer Facts & Figures-1997.(ACS Publication) Atlanta, GA.
2. Knobf MK, Mullen JC, Xistris D, Mortiz PA. Weight gain in women with breast cancer receiving adjuvant chemotherapy. Oncology Nursing Forum. 10:28-34, 1983.
3. Huntington MO. Weight gain in patients receivng adjuvant chemotherapy for carcinoma of the breast. Cancer. 56:472-474, 1985.
4. Boyd NF. Nutrition and Breast Cancer. J Natl Cancer Inst. 85:6-7, 1993.
5. Prozato P et al. Megasterol acetate:phase II study of a single daily adminstration in advanced breast cancer. Breast Cancer Res treat. 17:51-54, 1990.
6. Dixon J, Moritz D, and Baker F: Breast Cancer and Weight Gain; An Unexpected Finding. Oncology Nursing Forum 5:5-7, 1978.
7. Demark-Wahnefried W, Winer EP, and Rimer, BK: Why women Gain Weight With Adjuvan Chemotherapy for Breast Cancer. Journal of Clinical Oncology 11:1418-1429, 1993.
8. Levine EG, Racqynski JM, Carpenter JT: Weight Gain With Breast Cancer Adjuvant Treatment. Cancer 67: 1954-1959, 1991.
9. Camoriano JK, Loprinzi CL, Ingle JN, Therneau TM, Krook JE, and Veeder MH: Weight Change in Women Treated With Adjuvant Therapy or Observed Following Mastectomey for Node-Positive Breast Cancer. Journal of Clinical Oncology 8:1327-1334, 1990.
10. Chlebowski RT, Weiner JM, Reynolds R, et al: Long-term survival following relapse after 5-FU but not CMF adjuvant breast cancer therapy. Breast Cancer Research and Treatment 7:23-29, 1986.
11. Cruz JM, Muss HB, Brockschidt JK, Evans G. Weight changes in women with metastatic breast cancer treated with megasterol acetate: a comparison of standard versus high-dose therapy. Semin Oncol. 17:63-67, 1990.
12. Heasmand KZ, Sutherland HJ, Campbell JA, et al: Weight gain during adjuvant chemotherapy for breast cancer. Breast Cancer Research and Treatment 5:195-200.
13. Huntington MO: Weight Gain in Patients Receiving Adjuvant Chemotherapy for Carcinoma of the Breast. Cancer 56:472-474, 1985.
14. DeConti RC. Weight gain in the adjuvant chemotherapy of breast cancer. Proc Am Soc Clin Oncol. 1:73, 1982.
15. Goodwin PJ, Panzarella T and Boyd NF: Weight gain in women with localized breast cancer- a descriptive study. Breast Cancer Research and Treatment 11:59-66, 1988.
16. Bonadonna G, Valagussa P, and Rossi A: Ten-year experience with CMF based adjuvant chemotherapy in resectable breast cancer. Breast Cancer Research and Treatment 5:95-115, 1985.
17. Knobf M: Physical and psychological distress associated with adjuvant chemotherapy in women with breast cancer. 4:678-684, 1986.
18. Bastracchea J, Hortobagyi GN, Smith TL, Kau SC: Obesity as an Adverse Prognostic Factor for Patients Receiving Adjuvant Chemotherapy for Breast Cancer. Annals of Internal Medicine 119: 18-25, 1993.
19. Schapira DV, Kumar NB, Lyman GH, Cox CE: Obesity and Body Fat Distribution and Breast Cancer Prognosis. Cancer 67: 523-528, 1991.

20. Demark-Wahnefried W, et al. Reduced rates of metabolism and decresed physical activity in breast cancer patients receiving adjuvant chemotherapy. Am J Clin Nutr. 65:1495-501, 1997.
21. DeGeorge D, Gray JJ, Fetting JH, and Rolls BJ: Weight Gain in Patients With Breast Cancer Receiving Adjuvant Treatment as a Function of Restraint, Disinhibition, and Hunger. Oncology Nursing Forum (supp) 17:23-30, 1990.
22. Smets, EMA, Barssen ALJ, Schuster-Uitterhoeve ALJ, et al: Fatigue in cancer patients. British Journal of Cancer 68:220-224,1993.
23. Winningham ML, Nail LM, Burke MB, et al: Fatigue and the cancer ezperience: The state of knowledge. Oncology Nursing Forum 21: 23-26, 1994.
24. Demark-Wahnefried W,Rimer BK, Winer EP. Weight gain in women with breast cancer. J Am Diet Assn. 97:5519-526, 1997.
25. Fortin H, et al: Psychosomatic approach to premenstrual syndrome. Canadian Medical Association Journal 79:978-81, 1958.
26. Foltz AT: Weight Gain Among Stage II Breast Cancer Patients: A Study of Five Factors. Oncology Nursing Forum 12:21-26, 1985.
27. Rose D and Davies T: Ovarian function in patients receiving adjuvant chemotherapy for breast cancer. Lancet 1:1174-6,1977.
28. Morabia A, Szklo M, Sewart W, Schulman L, Thomas DB, Zacur HA: Thyroid hormones and duration of ovulatory activity in the etiology of breast cancer. Cancer Epidemiology, Biomarkers & Prevention 1: 389-93, 1992.
29. Clur A: Di-iodothyronine as part of the oestradiol and catechol oestrogen receptor-- the role of iodine, thyroid hormones and melatonin in the aetiology of breast cancer. Medical Hypotheses 27: 303-11, 1988.
30. Wade GN, Gray JM, Blausten JD: Effects of Estrogens and Antiestrogens on Eating Behavior, Metabolism, and Energy Balance 7(supp):61-68,1993.
31. denBesten C, Vansant G, Westrate JA, et al: Resting Metabolic rate and diet induced thermogenesis in abdominal and gluteal-femoral obese women before and after weight reduction. American Journal of Clinical Nutrition 47:840-847, 1988.
32. Haarbo J, Marslew U, Gotfredson A, et al: Postmenopausal hormone replacement therapy prevents central distrivution of vody fat after menopause. Metabolism 40:1323-1326, 1991.
33. Bisdee JT, James WPT, Shaw MA: Changes in energy expenditure during the menstrual cycle. British Journal of Nutrition 61:187,1989.
34. Solomon SJ, Kurzer MS, Calloway DH: Menstrual cycle and basal metabolic rate in women. American Journal of Clinical Nutrition 36: 611, 1982.
35. Segal Kr, Dunaif A: Resting Metabolic Rate and Postprandial Thermogenesis in Polycystic Ovarian Syndrome. International Journal of Obesity 14:559-67, 1990.
36. Sallis J, Haskell W, Wood P, et al. Physical activity assessment methodology in the Five-City project. Am J Epidemiol. 21:91-106, 1985.
37. McNair DM, Lorr M, Droppleman LF: The Manual for the Profile of Mood States. SanDiego CA: Educational and Industrial Testing Service 1971.
38. Folkman S, Lazarus RS: Analysis of coping in amiddle-aged community sample. Journal of Health and Social Behavior 21: 219-239, 1980.